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Ovarian cancer screening in the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial: Findings from the initial screen of a randomized trial

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Objective: Ovarian cancer screening with transvaginal ultrasound (TVU) and CA-125 was evaluated in the Prostate, Lung, Colorectal and Ovarian (PLCO) Trial.
Study design: This was a randomized controlled trial of screening versus usual care. Baseline screening results are reported.
Results: Of 39,115 women randomized to receive screening, 28,816 received at least 1 test. Abnormal TVU was found in 1338 (4.7%), and abnormal CA-125 in 402 (1.4%). Twenty-nine neoplasms were identified (26 ovarian, 2 fallopian, and 1 primary peritoneal neoplasm). Nine were tumors of low malignant potential and 20 were invasive. The positive predictive value for invasive cancer was 3.7% for an abnormal CA-125, 1.0% for an abnormal TVU, and 23.5% if both tests were abnormal.
Conclusion: The effect of screening on ovarian cancer mortality in the PLCO cohort has yet to be evaluated and will require longer follow-up. Screening identified both early- and late-stage neoplasms, and the predictive value of both tests was relatively low.

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Advances in the treatment of ovarian cancer in the past decade have led to incremental improvements in survival. For example, it is now known that initial surgery by an experienced gynecologic oncologist increases the likelihood of optimal debulking and is associated with an improved long-term survival rate.[1-3] The introduction of platinum-based, multiagent chemotherapy regimens, the more recent addition of the taxanes into clinical practice, the widespread use of salvage chemotherapy for recurrent cancer, and the increasing use of chemotherapy in less advanced stage disease have all contributed to improved survival.[4] Despite these advances, ovarian cancer remains a fatal disease for most women in whom it is diagnosed, and it has the highest mortality rate of all the gynecologic malignancies. Ovarian cancer is diagnosed in 25,400 women and results in 14,300 deaths annually in the US.[5] Most cases present at an advanced stage, and long-term survival is achieved in less than a third of patients. However, early stage ovarian cancer has a much higher survival rate, and it is possible that early detection through screening could significantly reduce mortality.

Screening for early disease is useful if the disease in question has a presymptomatic stage in which treatment is more effective than treatment administered for symptomatic disease. Effective screening also requires the availability of screening procedures acceptable to patients that can be performed at a reasonable cost. Finally, screening tests must have a sensitivity high enough to detect a significant fraction of all existing cases in the population and, at the same time, a sufficiently high specificity to avoid generating an excessive number of false-positive screens. False-positive test results are a particular problem in diseases with low prevalence in the target population and in diseases for which further evaluation of an abnormal screen often includes an invasive surgical procedure. Both concerns are true for ovarian cancer. One method to address the problem of balancing sensitivity and specificity is to utilize more than 1 screening test in combination, either in parallel or sequentially.

Bimanual palpation of the ovaries is widely used to detect ovarian pathology, but it is insensitive for detection of early stage cancer, and its widespread application has not resulted in a significant shift to earlier-stage ovarian cancer.[6] Both CA-125 and ultrasound, particularly transvaginal ultrasound (TVU), have been advocated as potential ovarian cancer screening modalities. TVU screening has generally been associated with a high rate of false-positive screens, leading to a large number of surgical procedures that did not identify cancer.[7-9] CA-125 is reported to be elevated in about half of women with early-stage ovarian cancer, but it is also increased in other cancers and in various nonmalignant conditions such as liver disease and heart failure.[10-13] Studies to date have not clarified the efficacy of TVU and CA-125, performed either separately or together, for ovarian cancer screening.[14] In this report, we describe the characteristics of the 39,115 women randomized to the screened arm of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial and report the results of the initial (baseline) ovarian cancer screening examinations in 28,816 women. TVU and CA-125 were performed at study entry and were administered concurrently.

Material and methods

Study design

The design of the PLCO Trial has been described in detail elsewhere.[15] Briefly, the objectives are to determine in healthy subjects aged 55-74 at entry whether: 1) screening with flexible sigmoidoscopy can reduce mortality from colorectal cancer in males and females; 2) screening with chest x-ray can reduce mortality from lung cancer in males and females; 3) screening with digital rectal examination plus serum prostate specific antigen (PSA) can reduce mortality from prostate cancer; and 4) screening with CA-125 and transvaginal ultrasound can reduce mortality from ovarian cancer.

The study is a 2-armed trial in which half of subjects were randomized to receive screening, and half to usual care. Enrollment was initiated in the fall of 1993 and completed in the summer of 2001. Ten screening centers are participating: the University of Colorado Health Sciences Center; Lombardi Cancer Research Center of Georgetown University; Pacific Health Research Institute, Honolulu; Henry Ford Health System; University of Minnesota School of Public Health/Virginia L. Piper Cancer Institute; Washington University School of Medicine; University of Pittsburgh, Pittsburgh Cancer Institute and Magee-Women's Hospital; University of Utah Health Sciences Center; Marshfield Clinic Research Foundation; and the University of Alabama at Birmingham. Each institution obtained local Institutional Review Board approval to carry out the study. CA-125 and PSA testing is performed centrally at the University of California, Los Angeles Immunogenetics Center. A biorepository for the collection and storage of blood samples and tissue is an integral component of the trial. Participants will be followed for at least 13 years from entry.

Women in the intervention arm are screened for ovarian cancer using CA-125 annually for 6 years and TVU annually for 4 years. Both studies are performed concurrently at entry into the study. Baseline ovarian cancer screening tests were performed on the first randomized subject on November 15, 1993 and on the last subject on December 13, 2001. The screening protocol originally included bimanual physical exam of the ovaries as one of the screening modalities. This

procedure was dropped in 1998 after review of the data determined that no ovarian cancers had been detected with this modality alone. This experience is consistent with previous reports suggesting that pelvic examination is not a satisfactory screening tool for ovarian cancer.[6] In addition, more than two thirds of all women entering the study had routine bimanual pelvic examinations as part of their ongoing medical care, thus compromising our ability to compare the impact of bimanual examination on ovarian cancer mortality between the screened and unscreened arms.

Eligibility

The target population for the study included subjects from 55 to 74 years of age who had not been diagnosed previously with prostate, lung, colorectal, or ovarian cancer. Criteria for exclusion included current treatment for cancer other than basal cell and squamous cell skin cancer, and enrollment in another cancer screening or prevention trial. Beginning on April 15, 1995, individuals who had received a colonoscopy, sigmoidoscopy, or barium enema in the past 3 years were excluded. Women on tamoxifen were initially excluded because, at the time of study initiation, the relationship between tamoxifen and ovarian cancer risk was unknown. This restriction was lifted in April 1999 when it became clear that this was a null association.[16] Individuals with previous surgical removal of 1 lung or the entire colon were also excluded. Initially, women who had undergone oophorectomy were ineligible but in 1996 this restriction was lifted because low accrual of women threatened to jeopardize screening end points for lung and colon cancer. Women who had undergone oophorectomy were not offered either ovarian cancer screening test.

Screening procedures

TVU was performed by qualified sonographers using a 5-7.5 MHz transvaginal probe. The examiner imaged both ovaries in the transverse and longitudinal planes. At least 5 minutes were spent looking for each ovary to ensure an adequate search; however, if the iliac vessels were visualized without ovaries being seen the examiner concluded the search for the ovaries.[17] Ovaries were measured along the major and minor axes in both transverse and longitudinal planes, and the prolate ellipsoid formula (width $\times$ height $\times$ thickness $\times$ 0.523) was used to calculate the volume of each ovary and/or cyst. The following TVU test results were classified as abnormal (positive): ovarian volume >10 cm^3; cyst volume >10 cm^3; any solid area or papillary projection extending into the cavity of a cystic ovarian tumor of any size; or any mixed (solid/cystic) component within a cystic ovarian tumor.

CA-125 was measured on serum obtained and frozen within 2 hours of blood draw at each of the 10 screening centers, then shipped to the UCLA Immunogenetics Center on dry ice. Samples were stored at -70°C and aliquots thawed for assay. Assays were performed according to the instructions from the manufacturer (Centocor, Inc, Malvern, PA). Samples were run in duplicate. Any sample with a result over 35 U/mL was reanalyzed to verify the value. Samples showing discrepant results between duplicate results (coefficient of variation over 10%) were reanalyzed. Quality assurance for the measurement of CA-125 was done in accordance with the manufacturer's suggested protocol using manufacturer-supplied samples, as well as additional control samples obtained from Bio-Rad (Hercules, CA). The assay precision is represented by its coefficient of variation (CV). The CVs (and 95% CIs) were found to be 4.07% (3.92-4.22) at the lower concentration of 52.7 U/mL and 3.78% (3.64-3.92) at the higher concentration of 106.5 U/mL. These results are in good agreement with those reported by the manufacturers on the product inserts.

The original Centocor CA-125 radioimmunoassay (RIA) assay was replaced with the Centocor CA-125II RIA assay on October 1, 1995. All samples tested using the original CA-125 assay were retested using the CA-125II assay. Of 5371 samples analyzed with both tests, the mean value rose from 9.4 to 13.1 U/mL. One hundred and twenty-two samples changed screening results, with 109 converting from negative to positive with the new assay (2.0%). Three of these subjects were diagnosed with cancer after the baseline screen; all 3 had an abnormal TVU. Four of the other 106 subjects also had an abnormal TVU but did not have ovarian cancer. Thirteen samples converted from positive to negative (0.24%). None of these subjects were diagnosed with ovarian cancer. The original CA-125 had a positivity rate of 0.6%, and the CA-125II assay had a positivity rate of 2.4% in these 5371 samples.

CA-125 results ≥ 35 U/mL were classified as abnormal (positive).

Results of both screening tests were sent to participants and their personal physicians within 3 weeks of specimen submission. Evaluation and follow-up of women with an abnormal screening test were at the discretion of the participant's physician.

Follow-up of abnormal screening tests

Medical records of all procedures done to evaluate an abnormal screen were obtained by study personnel and recorded on standardized reporting forms. Pathology reports from all ovarian neoplasms were abstracted by trained certified tumor registrars and were reviewed by one of the authors (E.P.). Neoplasms with an ICD-O-2 behavior code of 3 (malignant neoplasms) and diagnosed in the screened arm within 12 months of a positive baseline screen are included in this report. (The NCI's Surveillance, Epidemiology and End Results Program

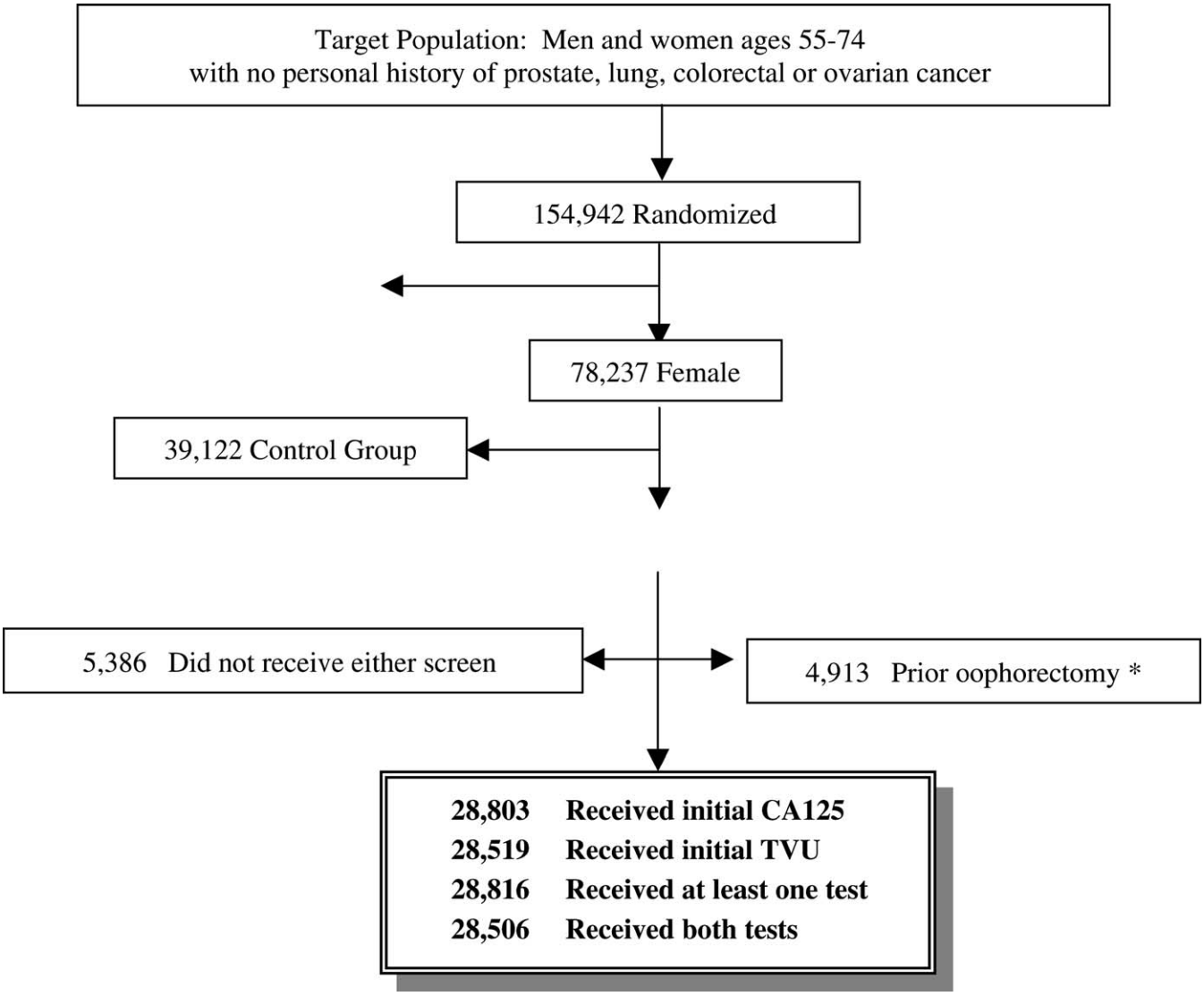

Figure Flow of participants into the PLCO Trial. *Ineligible for screening.

considers those neoplasms with a behavior of either 2 or 3 to be reportable as cancer.) Ovarian tumors occurring among women in the control group are not reported here. The purpose of this paper is to report on the performance characteristics of CA-125 and TVU in an initial screen.

Results

Enrollment

Enrollment into the PLCO Trial is shown in the Figure. Of 78,237 females enrolling into the trial, 39,115 were randomized to the intervention arm. Of these, 4913 women reported previous oophorectomy and were not eligible for ovarian screening, and an additional 5386 did not receive either screen. Of the 5386 who had neither screen, 3 were diagnosed with ovarian cancer before receiving screening; 17 died before any screening; 105 withdrew from the study; 5232 refused all T0 PLCO screening procedures; and 29 underwent other PLCO T0 procedures but refused ovarian cancer screening. Thirteen underwent TVU but not phlebotomy, and 297 had CA-125 measured but no TVU. Thus, a total of 28,816 women received at least 1 screening test and 28,506 received both. This report describes the characteristics of the 39,115 women randomized to the intervention arm, and summarizes the results in 28,803 women who received the initial CA-125 measurement and 28,519 who received the initial TVU.

Baseline characteristics

At study entry, subjects completed a baseline questionnaire that included age, race, educational level, and specific risk factors for ovarian cancer, including previous

Table I Characteristics of participants in the intervention arm

	Screened		Not screened		Previous oophorectomy	
	Number	%	Number	%	Number	%
Age group						
55–59	9974	34.6	1698	31.5	1787	36.4
60–64	8871	30.8	1533	28.5	1370	27.9
65–69	6242	21.7	1251	23.2	1095	22.3
70–74	3729	12.9	904	16.8	661	13.5
Race						
White	25,618	88.9	3868	71.8	4342	88.4
Black	1533	5.3	356	6.6	281	5.7
Hispanic	417	1.4	93	1.7	95	1.9
Asian	984	3.4	159	3.0	116	2.4
Other	200	0.7	51	0.9	32	0.7
Missing response	64	0.2	859	15.9	47	1.0
Education level						
<High school	1685	5.8	483	9.0	352	7.2
12 y/completed high school	11,427	39.7	1866	34.6	2006	40.8
Some college	6587	22.9	1086	20.2	1238	25.2
College graduate	4624	16.0	545	10.1	659	13.4
Postgraduate	4405	15.3	523	9.7	609	12.4
Missing response	88	0.3	883	16.4	49	1.0
Had previous pelvic surgery						
Bilateral oophorectomy	2	0.0	3	0.1	59	1.2
Hysterectomy	7768	27.0	1098	20.4	199	4.1
Bilateral oophorectomy and hysterectomy	83	0.3	105	1.9	4601	93.6
Neither	20,811	72.2	3295	61.2	8	0.2
Missing response	152	0.5	885	16.4	46	0.9
Ever taken oral contraceptives						
No	13,168	45.7	2327	43.2	2127	43.3
Yes	15,554	54.0	2175	40.4	2736	55.7
Missing response	94	0.3	884	16.4	50	1.0
Number of times pregnant						
None	2084	7.2	384	7.1	371	7.6
1	1640	5.7	253	4.7	309	6.3
2	5091	17.7	782	14.5	887	18.1
3-4	11,729	40.7	1738	32.3	1988	40.5
5-9	7625	26.5	1244	23.1	1232	25.1
10 or more	539	1.9	114	2.1	72	1.5
Missing response	108	0.4	871	16.2	54	1.1
Personal history of breast cancer						
No	27,718	96.2	4381	81.3	4718	96.0
Yes	1040	3.6	148	2.7	150	3.1
Missing response	58	0.2	857	15.9	45	0.9
Family history of breast and ovarian cancer						
Neither	23,517	81.6	3732	69.3	3964	80.7
Breast cancer	3623	12.6	547	10.2	629	12.8
Ovarian cancer	948	3.3	128	2.4	175	3.6
Breast and ovarian cancer	120	0.4	13	0.2	30	0.6
Missing response	608	2.1	966	17.9	115	2.3
Had baseline questionnaire						
No	54	0.2	855	15.9	45	0.9
Yes	28,762	99.8	4531	84.1	4868	99.1
Total	28,816	100.0	5386	100.0	4913	100.0

gynecologic surgery, use of oral contraceptives, parity, personal history of breast cancer, and family history of breast and ovarian cancer in first-degree relatives. Data from the baseline questionnaire are shown for the 39,115 women randomized to the intervention arm (Table I). Table I is divided into 3 groups: those who received any

Table II CA-125 and TVU screening results combinations

CA-125		TVU +	TVU −	Total
+	#	34	365	399
	%	0.1	1.3	1.4
−	#	1304	26,803	28,107
	%	4.6	94.0	98.6
Total	#	1338	27,168	28,506
	%	4.7	95.3	100.0

Only women having results for both TVU and CA-125 appear in this table. Three hundred and ten subjects were excluded from table because they had only 1 of the screening tests.

Table III CA-125 and TVU results for confirmed neoplasms

Neoplasm type	CA-125	TVU	#	%
Low Malignant Potential	+	+	1	3.4
	−	+	8	27.6
Granulosa	−	+	1	3.4
Invasive Ovarian	+	+	7	24.1
	−	+	4	13.8
	+	−	5	17.2
Fallopian Tube	+	+	1	3.4
	+	−	1	3.4
Peritoneal	+	−	1	3.4
Total			29	100.0

baseline ovarian cancer screening; those who did not receive either baseline ovarian cancer screen; and those who were ineligible for screening because of previous oophorectomy. Women provided information about previous oophorectomy both as part of the baseline questionnaire ("had previous pelvic surgery" on Table I) and at the time ovarian cancer screening was scheduled. Women who at that time reported that they were not eligible for ovarian cancer screening because of previous oophorectomy ("previous oophorectomy" on Table I) did not receive ovarian cancer screening regardless of their report on the baseline questionnaire; similarly, women who reported no previous oophorectomy received screening despite their conflicting baseline questionnaire report. For this reason there are some inconsistencies in Table I. Women in the "not screened" group were on average older than those in the other 2 groups and were less educated. They also had a higher rate of noncompliance with the baseline questionnaire (15.9%) than women in the screened (0.2%) or oophorectomy (0.9%) groups. Enrollment declined with advancing age, with subjects aged 55 to 59, 60 to 64, 65 to 69, and 70 to 74 years comprising 34.4%, 30.1%, 22.0%, and 13.5% of participants, respectively. Subjects were primarily white (86.5%) and educated (over 50% reported having at least some college education). Although some women did not complete the baseline questionnaire or did not answer questions about gynecologic surgery, data were collected from over 97% of the participants.

Compliance

Compliance rates for the baseline screening procedures were 83.4% for TVU and 84.2% for CA-125. The rate of compliance with each screening test declined slightly with advancing age; among subjects 55 to 59 and 70 to 74 years of age, compliance rates were 84.5% and 79.5%, respectively, for TVU, and 85.5% and 80.5%, respectively, for CA-125. Women who did not have a screen because of previous oophorectomy were excluded from the compliance calculations.

Screening results

The baseline TVU was abnormal in 1338 (4.7%) of 28,519 baseline examinations. As previously reported,[18] the ability of the examiner to visualize the ovaries by TVU decreased with advancing age of the participant, but age otherwise had no effect on TVU results (data not shown). A small number of examinations (1.9%) were classified as inadequate for interpretation.

Abnormal values for CA-125 were found in 402 (1.4%) of 28,803 baseline measurements. Age had a minimal effect on CA-125 concentration. Three fourths of the CA-125 values in each age group fell between 5 and 15 U/mL. A small number of samples (0.3%) contained insufficient serum to perform the assay.

At the individual level, there was very little overlap in abnormal results for the 2 screening tests (Table II). Among 28,506 women with results for both tests, 1703 had at least 1 abnormal test; 1338 had an abnormal TVU, 399 had an abnormal CA-125, and only 34 (2% of those with an abnormal screen) had abnormalities in both.

As a result of the baseline screening examination and subsequent follow-up procedures, 29 malignant neoplasms were identified (Table III). Twenty-six arose in the ovary, 9 of which were tumors of low malignant potential, 1 was an ovarian stromal tumor (granulosa cell), and 16 were invasive epithelial ovarian cancers. Three additional epithelial neoplasms were identified, 2 arising in the fallopian tube and 1 in the peritoneum. All 29 are designated "ovarian neoplasms" for subsequent analyses.

Table III shows the relationship between CA-125 and TVU results and ovarian neoplasms. Invasive cancers and tumors of low malignant potential are shown separately. CA-125 alone was abnormal in 7 (24%), and TVU alone was abnormal in 13 (45%). Both tests were abnormal in 9 subjects (31%).

An additional 25 subjects had abnormalities in both TVU and CA-125 during the initial examination. Seventeen of these had surgery with benign findings, and the

Table IV Histopathologic type, histopathologic grade, and stage by screening results

Primary site	Invasive	Histopathology	Grade	Stage	Screen results	CA-125 result	Days between pos screen and diagnosis
Ovary	No	Serous cystadenoma	LMP*	IA	TVU positive	15	221
Ovary	No	Serous cystadenoma	LMP*	IA	CA-125 & TVU +	51	79
Ovary	No	Serous cystadenoma	LMP*	IA	TVU positive	18	55
Ovary	No	Serous cystadenoma	LMP*	IA	TVU positive	26	30
Ovary	No	Serous cystadenoma	LMP*	IA	TVU positive	8	91
Ovary	No	Serous cystadenoma	LMP*	IA	TVU positive	15	39
Ovary	No	Mucinous cystadenoma	LMP*	IA	TVU positive	17	46
Ovary	No	Serous cystadenoma	LMP*	IC	TVU positive	28	23
Ovary	No	Serous cystadenoma	LMP*	IC	TVU positive	26	80
Ovary	Yes	Malignant granulosa	Grade III	IA	TVU positive	8	316
Ovary	Yes	Serous cystadenocarcinoma	Grade III	IB	CA-125 & TVU +	793	40
Ovary	Yes	Serous cystadenocarcinoma	Grade II	IIA	TVU positive	13	213
Ovary	Yes	Papillary serous & endometrial	Grade III	IIC	CA-125 & TVU +	456	42
Ovary	Yes	Endometrioid adenocarcinoma	Grade III	IIIA	TVU positive	15	157
Ovary	Yes	Serous cystadenocarcinoma	Grade III	IIIB	TVU positive	9	72
Ovary	Yes	Adenocarcinoma, NOS	Grade III	IIIB	CA-125 positive	1260	49
Ovary	Yes	Serous cystadenocarcinoma	Grade III	IIIC	CA-125 & TVU +	1556	65
Ovary	Yes	Serous cystadenocarcinoma	Grade III	IIIC	CA-125 positive	2182	76
Ovary	Yes	Serous cystadenocarcinoma	Grade II	IIIC	CA-125 & TVU +	73	34
Ovary	Yes	Serous cystadenocarcinoma	Grade III	IIIC	CA-125 positive	406	49
Ovary	Yes	Serous cystadenocarcinoma	Grade III	IIIC	CA-125 positive	875	80
Ovary	Yes	Adenocarcinoma	Grade III	IIIC	CA-125 & TVU +	1143	104
Ovary	Yes	Mucin-producing adenocarcinoma	Grade III†	IIIC	CA-125 positive	78	44
Ovary	Yes	Papillary adenocarcinoma	Grade III	IIIC	CA-125 & TVU +	123	23
Ovary	Yes	Carcinoma, NOS	Grade III	IIIC	CA-125 & TVU +	410	59
Ovary	Yes	Serous cystadenocarcinoma	Grade III	IV	TVU positive	31	237
Fallopian Tube	Yes	Endometrioid adenocarcinoma	Grade III	IIB	CA-125 & TVU +	96	21
Fallopian Tube	Yes	Papillary adenocarcinoma, NOS	Grade III	IV	CA-125 positive	85	96
Peritoneum	Yes	Carcinoma, NOS	Grade III	IIIC	CA-125 positive	69	83

* Low malignant potential.
† Grade determined from metastasis.

8 who did not have surgery were not diagnosed with cancer during the subsequent 12 months.

Table IV shows the characteristics of tumors detected during the baseline screen. The 9 tumors of low malignant potential were all stage I, as was the malignant granulosa cell tumor. The stages of the 19 invasive epithelial tumors included 1 stage I, 3 stage II, 13 stage III, and 2 stage IV.

Table IV also shows the time interval between the positive screening test and the diagnosis of cancer. The PLCO protocol allowed up to 3 weeks between the screening test and results being sent to the physician. Further evaluation and follow-up resulted in a lengthy delay in surgery for some subjects; however, only 5 of the 29 cases had a delay of over 120 days from the initial screen to surgery. These included a stage IA serous cystadenoma (221 days), a stage IA malignant granulosa tumor (316 days), a stage IIA serous cystadenocarcinoma (213 days), a stage IIIA endometrioid adenocarcinoma (157 days), and a stage IV serous cystadenocarcinoma (237 days). In each of these cases the TVU result was positive but the CA-125 was normal. This delay could have contributed to the high stage of some of the neoplasms, particularly the stage IV serous cystadenocarcinoma.

The positive predictive value (PPV) of each test, and of the 2 tests together, was calculated (Table V). For example, 28,803 women had a CA-125 test, 402 of which were abnormal (1.4%). Sixty-two women underwent biopsy (15.4% of positive screens), 16 of which (25.8% of biopsies) were diagnosed with a neoplasm, for a PPV of 4.0% (16 neoplasms in 402 positive screens). Similar calculations demonstrate a PPV of 1.6% for TVU, and 26.5% if both tests were abnormal. Table V also shows similar data excluding tumors of low malignant potential (indicated as "# invasive cancer"). With this restriction, the PPV was 3.7% for an abnormal CA-125, 1.0% for an abnormal TVU, and 23.5% if both tests were

Table V Follow-up of positive screens

	Exam			
	CA-125	TVU	Both exams*	Either exam†
# Screened (A)	28803	28519	28506	28816
# Screen positives (B)	402	1338	34	1706
% of screened having positive result (B/A × 100)	1.4	4.7	0.1	5.9
Rate positive per 1000 screens (B/A × 1000)	13.9	46.9	1.1	59.2
# Biopsies (C)	62	535	27	570
% of positive screens having a biopsy (C/B × 100)	15.4	40.0	79.4	33.4
Rate biopsied per 1000 screens (C/A × 1000)	2.1	18.7	0.9	19.7
# Neoplasms diagnosed (D)	16	22	9	29
% of biopsies showing a neoplasm (D/C × 100)	25.8	4.1	33.3	5.1
PPV of screening test (D/B × 100)	4.0	1.6	26.5	1.7
Rate neoplasms diagnosed per 1000 screens (D/A × 1000)	0.5	0.7	0.3	1.0
# Surgeries per neoplasm diagnosed (C/D)	3.9	24.3	3.0	19.7
# Invasive cancers diagnosed (E)	15	13	8	20
% of biopsies showing invasive cancer (E/C × 100)	24.2	2.4	29.6	3.5
PPV of screening test (E/B × 100)	3.7	1.0	23.5	1.2
Rate cancer diagnosed per 1000 screens (E/A × 1000)	0.5	0.4	0.2	0.6
# Surgeries per invasive cancer diagnosed (C/E)	4.1	41.2	3.4	28.5

For this table: Screen positive (B) implies screened (A), biopsied (C), implies screen positive (B), neoplasms diagnosed (D), implies biopsied (C), and cancer diagnosed (E) implies biopsied (C). All biopsies were performed surgically, either laparoscopically with or without a vaginal approach (n = 245) or with a laparotomy (n = 325).

* Both exams: # screened (A) represents total participants that received both screens, and # screen positives (B) represents participants that had both screens positive.

† Either exam: # screened (A) represents total participants that received either screen, and # screen positives (B) represents participants that had either screen positive.

abnormal. In this table, all biopsies were performed surgically, either with laparoscopy or laparotomy, as indicated in the table legend.

Follow-up diagnostic procedures

All participants with at least 1 abnormal screening result (n = 1706) were tracked to assess the diagnostic procedures performed as a consequence of an abnormal screening test result. Because the PLCO protocol did not mandate specific evaluation of a woman with positive screens, follow-up procedures up to and including surgery were at the discretion of the patient's physician. Each subject and their physician received a letter that notified them of the positive screen and the recommendation to obtain follow-up, but some subjects (about 15%) did not have further evaluation of a positive screen. Follow-up procedures are summarized in Table VI. Of importance, 570 women underwent a surgical procedure (325 laparotomy and 245 laparoscopy and/or vaginal approach), including 541 who proved not to have a neoplasm. Thus, 541 of 1706 subjects (31.7%) who had at least 1 positive screening test underwent surgery but did not have cancer.

Comment

Screening to detect early-stage ovarian cancer is theoretically appealing because this malignancy is typically heralded by vague, nonspecific symptoms and is characterized by advanced stage at diagnosis. This report of the initial ovarian cancer screen in women aged 55 to 74 who volunteered to participate in the PLCO study demonstrates some of the practical difficulties inherent in screening for diseases with a low prevalence in the target population.

We screened 28,816 women and detected 29 neoplasms, or 1 neoplasm for every 994 subjects screened. Nineteen were invasive epithelial cancers, or 1 cancer for every 1517 subjects screened. The cancers were identified among 1338 women who had an abnormal TVU (4.7% of all women screened) and 402 who had an abnormal CA-125 (1.4% of all women screened). Diagnostic evaluation of these abnormalities included not only relatively benign (although expensive and anxiety-provoking) radiographic procedures, but also 570 surgical procedures, including 325 laparotomies. When used alone, the positive predictive value of TVU for invasive cancer was 1.0%, and for CA-125 it was 3.7%. The PPV of TVU in our study was lower than in previous studies,[8,9] possibly because of the multicenter nature of the PLCO trial. TVU results from studies conducted with a single or a limited number of ultrasonographers may have a higher PPV. On the other hand, the PPV of CA-125 in the PLCO trial was higher than in other studies. PLCO subjects were all 55 years of age or older and, therefore, almost exclusively postmenopausal. Premenopausal women, who were included in most

Table VI Participant-based diagnostic procedures following a positive screen

	No neoplasm		Neoplasms	
Diagnostic procedures	n	%	n	%
CA-125	377	22.5	12	41.4
Ultrasounds	721	43.0	12	41.4
Chest radiograph	68	4.1	7	24.1
Surgery*	541	32.3	29	100.0
CT scan/MRI	150	8.9	12	41.4
Needle aspiration, culdocentesis, or paracentesis	22	1.3	1	3.4
IVP	8	0.5	·	·
Barium enema	7	0.4	·	·
No diagnostic procedure recorded	260	15.5	·	·
Total number of participants	1677	100.0	29	100.0

* Two hundred ninety-eight of the surgeries of the participants without neoplasms were a laparotomy; 27 of the surgeries of the participants with neoplasms were a laparotomy.

previous studies of screening, have a larger number of false positive CA-125 values than older women. Not surprisingly, an abnormal TVU resulted in a higher rate of surgeries (535 of 1338, or 40%) than an abnormal CA-125 (62 of 403, or 15.4%). Knowing that many other (nonmalignant) conditions may influence CA-125 levels, it is harder to justify performing surgery in an asymptomatic subject with an elevated CA-125 than in a similar patient with an adnexal mass found on TVU. Abnormalities in both tests were found in only 34 subjects, in whom the PPV for the 2 tests combined was 23.5%. However, if one chose to evaluate only subjects in whom both screening tests were abnormal, 20 of the 29 ovarian neoplasms (and 12 of the 20 invasive cancers) would have been missed. We identified 1 neoplasm for every 20 surgical procedures performed. If surgery was done to evaluate an abnormal CA-125, 1 neoplasm was identified per 3.9 surgeries (16 of 62), whereas 24 surgeries were required to identify 1 neoplasm based on an abnormal TVU (22 of 535). One neoplasm was found per 3 surgeries (9 of 27) if both TVU and CA-125 were abnormal.

Almost 2% of women who were screened at the time of entry into the PLCO trial (570 of 28,816) underwent abdominal surgery in the course of evaluating abnormalities detected by the PLCO ovarian cancer screening strategy. Several factors may have contributed to the high rate of pelvic surgery among the women in this series. 1) Many of the subjects may have had previously existing indications for elective pelvic surgery (bladder dysfunction, etc), with the finding of an abnormal TVU or CA-125 simply being the final impetus for performing the procedure. 2) Follow-up may have been particularly aggressive because subjects were part of a national cancer screening study, and physicians may have felt that their medical decisions would be closely scrutinized. However as noted above, 15% of subjects with a positive screen had no follow-up. 3) Ovarian screening with TVU and CA-125 is not done routinely, and the false-positive rate is not as well defined as that for other more common screening procedures. Because ovarian cancer is notoriously a highly lethal disease, physicians may not have been comfortable with a "watch and wait" approach to those with an abnormal screening test. 4) The definitive diagnostic test for an abnormal ovary seen on TVU is oophorectomy. Percutaneous biopsy is not utilized as routinely for diagnosis of ovarian masses as it is for many other organs, because of the risk of false-negative studies and the theoretical possibility of seeding the peritoneum with cancer cells if the biopsied lesion proves to be malignant. 5) Hysterectomy with or without oophorectomy has been performed very commonly in the past, particularly among women in the PLCO age range. By way of illustration, 35.6% of women enrolling in the PLCO Trial (13,918 of 39,115; see Table I) had undergone hysterectomy and/or oophorectomy before joining the study. Additionally, oophorectomy can often be done by laparoscopy. Physicians therefore may have had a low threshold for recommending this common procedure.

In addition to the invasive tumors, 9 cystadenomas of low malignant potential ("borderline") tumors were identified, representing 31% of the total malignant neoplasms found. This entity typically comprises only about 15% of all ovarian tumors as they present clinically in the general population.[19] While the number of cancer cases in this report is small, this observation suggests that screening as performed in the PLCO Trial, particularly with TVU, may preferentially detect low-grade tumors. This "length" bias (ie, slowly growing tumors are more likely than rapidly growing tumors to be detected with screening) has the ultimate effect of finding neoplasms that might go undetected for the lifetime of the patient, and therefore, not contribute to cancer mortality ("overdiagnosis"). Using mortality as the end point of a screening trial (as will be done for the PLCO study when follow-up is complete) eliminates the length bias. The detection of ovarian tumors of low malignant potential is unlikely to affect ovarian cancer mortality, since even stage III borderline tumors have a 90% 10-year disease-free survival.[20] Because only data from the initial (baseline) ovarian cancer screen have been analyzed thus far, the effect of repeated annual screens on detection rates and mortality, as is the protocol in the PLCO Trial, is currently unknown. The predictive value of these tests may be improved if post hoc analysis identifies a specific pattern of change over time in either TVU or CA-125 results, or if the combination of a specific TVU imaging pattern and a relatively high CA-125 correlates with a greater likelihood of having ovarian cancer. Fifteen of the 19 invasive neoplasms (79%) found

with the initial (prevalent) screen were stage III or IV cancers. Now that these high-stage cancers have been removed from the screened population, it is possible that subsequent screens will identify a group of early stage ovarian cancers with improved survival.

Further follow-up from the PLCO Trial will provide valuable data regarding the effect of annual screening on ovarian cancer mortality. At the present time, nothing in the findings reported here suggests a need to revise the present (1996) ovarian cancer screening guidelines of the US Preventive Services Task Force,[21] which state "routine screening for ovarian cancer by ultrasound, the measurement of serum tumor markers, or pelvic examination is not recommended."

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